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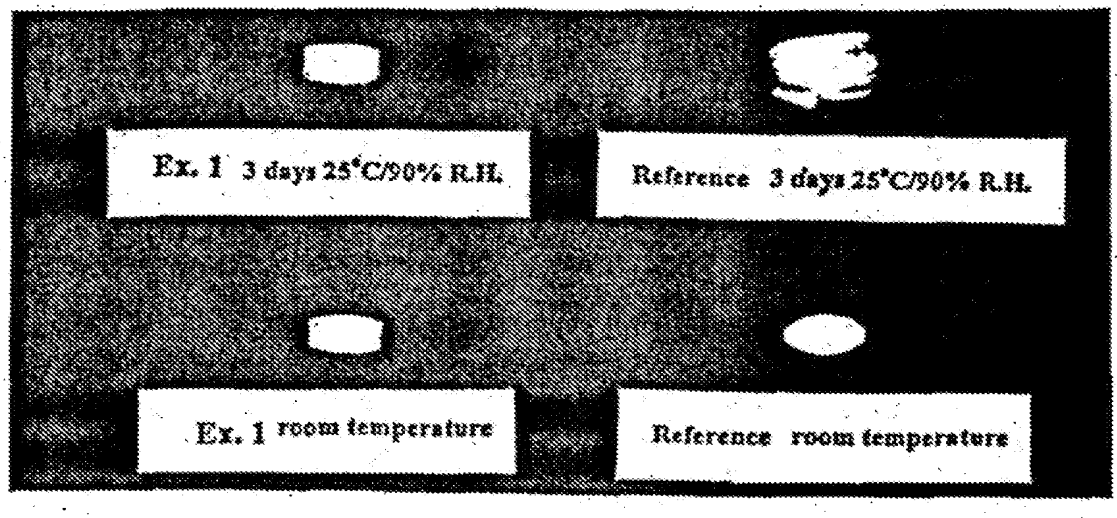

(57) Abstract

A sustained release pharmaceutical formulation is provided that has reduced sensitivity to moisture and thus enhanced storage stability. The formulation comprises a tablet containing a pharmacologically active agent and a carrier selected from the group consisting of solid polyethylene glycols, ingestible waxes, and mixtures thereof, with a carrier consisting essentially of a mixture of a solid polyethylene glycol and an ingestible wax preferred. Active agents include analgesics, particularly tramadol hydrochloride. Therapeutic methods are provided as well.

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SUSTAINED RELEASE FORMULATION WITH REDUCED MOISTURE SENSITIVITY

TECHNICAL FIELD

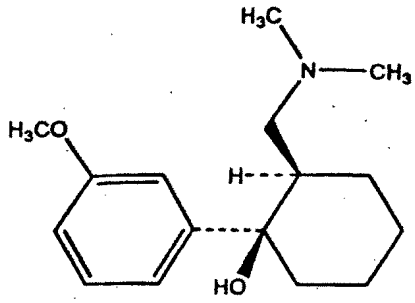
This invention relates generally to pharmaceutical formulations for oral administration, and more particularly relates to a sustained release pharmaceutical formulation with reduced sensitivity to moisture. The invention additionally relates to therapeutic methods wherein the novel sustained release formulation is administered to a patient.

BACKGROUND

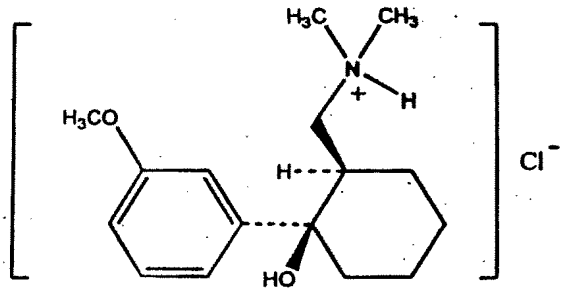
There are several forms of sustained release pharmaceutical compositions. One popular form includes prepared time capsules that contain tiny particles of the pharmaceutically active ingredient coated with layers of varying thicknesses. These coatings permit delayed release of the pharmaceutically active ingredient over a given time period. The particles with a thinner coating release the pharmaceutically active ingredient earlier whereas the particles with a thicker coating release the pharmaceutically active ingredient later. Thus, sustained release of the pharmaceutically active ingredient is achieved.

Another way to obtain a sustained release pharmaceutical composition is to prepare tablets that contain a pharmaceutically active ingredient dispersed in a matrix. The matrix forms a continuous phase around the pharmaceutically active ingredient and permits gradual release thereof. One of the problems with such sustained release formulations, i.e., formulations in which the active ingredient is present within a matrix, is moisture sensitivity. When such dosage forms are stored in a humid environment, they may disintegrate and thus the sustained release capability of the formulation is reduced or lost.

Tramadol hydrochloride, *trans*-(±)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride, is an analgesic that is effective against severe and moderately severe pain.



TRAMADOL



TRAMADOL HYDROCHLORIDE

Tramadol hydrochloride was first made available on the market in immediate release form. However, tramadol hydrochloride has recently become available, in Europe, in sustained release form (e.g., as Tramal® Long 100, from Grunenthal GmbH). In addition, U.S. Patent 5,601,842 to Bartholomaeus discloses a sustained release drug formulation containing tramadol hydrochloride in a cellulosic matrix.

There are several advantages to orally administering tramadol hydrochloride in sustained release form to a patient in need of analgesic medication. These advantages include the capability of administering fewer tablets in a given day (e.g., only one or two tablets daily) and the ability to maintain a minimum effective level of active agent in the bloodstream. The sustained release tramadol hydrochloride tablets disclosed in U.S. Patent 5,601,842 possess such advantages so long as the tablets are stored in an environment of low humidity. However, if the sustained release tramadol hydrochloride is stored under more humid conditions (e.g., 90% relative humidity) even for a period as short as three days, the tablets will swell, break into layers, and become difficult to swallow without chewing. Chewing the sustained release tablets destroys their sustained release character and causes immediate release of the active agent.

In U.S. Patent 5,601,842, it is disclosed that the tramadol hydrochloride sustained release tablets may be simple tablets or coated tablets such as film-coated tablets or sugar-coated tablets. However, even such coated tablets do not show storage stability in a humid environment and suffer the same problems of swelling and breaking apart into layers as do uncoated tablets.

U.S. Patent 5,591,452 describes an alternative controlled release formulation of tramadol. Those formulations are generally cellulose-based, i.e., formulated with one or more cellulosic polymers, and there is no indication that such formulations would be stable in humid environments. Thus, there is a need to develop additional sustained release drug formulations, e.g., tramadol formulations, that are stable in a humid environment.

DISCLOSURE OF THE INVENTION

It is accordingly a primary object of the invention to address the aforementioned need in the art by providing a sustained release pharmaceutical formulation with reduced sensitivity to moisture.

It is another object of the invention to provide such a formulation in tablet form.

It is yet another object of the invention to provide such a formulation that exhibits storage stability, even in humid environments.

It is an additional object of the invention to provide such a formulation that not only exhibits storage stability under humid conditions, but at the same time exhibits a satisfactory dissolution profile thereby.

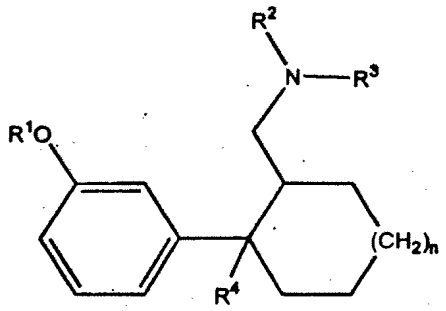
It is a further object of the invention to provide such a formulation wherein the active agent is tramadol hydrochloride.

It is still a further object of the invention to provide a method for treating pain by orally administering to a patient a sustained release tramadol hydrochloride formulation as provided herein.

In a first embodiment, then, a sustained release pharmaceutical formulation for oral administration is provided, the formulation comprising a therapeutically effective amount of a pharmacologically active agent and a carrier selected from the group consisting of solid polyethylene glycols, ingestible waxes, and mixtures thereof, wherein the active agent has a melting point above the melting point of the carrier, and further wherein the active agent is chemically stable at the melting point of the carrier. The pharmaceutical formulation is free of cellulose and cellulose derivatives. An exemplary formulation contains an active agent useful as an analgesic, the active agent having the structural formula

(I)

(I)



wherein: R^1 is C_1-C_3 alkyl or aralkyl, particularly phenyl lower alkyl, such as benzyl or phenethyl; R^2 and R^3 are C_1-C_6 alkyl, aralkyl, particularly phenyl lower alkyl, or R^2 and R^3 together with the nitrogen atom to which they are bound, form a morpholine or pyrrolidine ring; R^4 represents hydroxyl, halogen, or lower alkanoyloxy, particularly C_1-C_6 alkanoyloxy; and n is 0, 1 or 2, or a pharmaceutically acceptable acid addition salt thereof. It will be recognized, of course, that when R^1 is methyl, R^2 and R^3 are methyl, R^4 is hydroxyl and n is 1, the compound is tramadol.

In another embodiment, a method is provided for treating a patient by orally administering the present sustained release formulation within the context of a dosage regimen effective to treat a particular disorder or condition. In a preferred embodiment, the active agent is an analgesic agent such as tramadol hydrochloride, and the disorder or condition is pain.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1a is a top plan view of tablets of the formulation of Example 1 and Tramal® tablets after 3 days at room temperature and low humidity and at 25 °C and 90% relative humidity.

Figure 1b is a side view of the same tablets shown in Figure 1a.

MODES FOR CARRYING OUT THE INVENTION

OVERVIEW AND DEFINITIONS:

Before describing the present invention in detail, it is to be understood that unless otherwise indicated this invention is not limited to specific formulation components, manufacturing methods, dosage regimens, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, reference to "an active agent" includes a combination of two or more active agents, reference to "a carrier" includes a combination of two or more carriers, reference to "a solid polyethylene glycol" includes mixtures of solid polyethylene glycols (such as may have different molecular weight), reference to "an ingestible wax" includes mixtures of ingestible waxes, etc.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms "active agent," "drug" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical material or compound which, when administered to an organism (human or animal) induces a desired pharmacologic effect. Included are derivatives and analogs of those compounds or classes of compounds specifically mentioned that also induce the desired pharmacologic effect. The preferred active agents herein are analgesics, and the most preferred active agent is tramadol hydrochloride.

The term "sustained release" is used in its conventional sense to refer to a drug formulation that provides for gradual release of drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of drug over an extended time period.

By the terms "effective amount" or "therapeutically effective amount" of an agent as provided herein are meant a nontoxic but sufficient amount of the agent to provide the desired therapeutic effect. The exact amount required will vary from subject to subject,

depending on the species, age, and general condition of the subject, mode of administration, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

By "pharmacologically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any components of the pharmaceutical composition in which it is contained. Thus, a "pharmacologically acceptable" salt of a compound refers to a salt or ester that is not biologically or otherwise undesirable.

The term "stable" is used to refer to a formulation that is both physically and chemically stable over time, i.e., until the formulation is administered to a patient. Evidence of a "stable" formulation includes, for example, the absence of swelling, degradation, breakage, chemical transformation and other physical or chemical changes. The "stable" formulations herein do not swell, degrade, break, transform chemically, or otherwise undergo physical and/or chemical changes to any appreciable degree when stored for 72 hours at 25 °C at 90% relative humidity. It is preferred that when stored under the aforementioned conditions, at least about 90 wt.%, preferably at least about 95 wt.%, more preferably at least about 99 wt.%, and most preferably at least about 99.9 wt.% of the formulation will remain physically and chemically intact (i.e., physically and chemically unchanged).

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediaton of damage. Thus, for example, the present method of "treating" pain, as the term "treating" is used herein, encompasses both prevention of pain in a predisposed individual and treatment of an individual suffering from pain.

The following definitions pertain to chemical structures, molecular segments and substituents:

The term "alkyl" as used herein refers to a branched or unbranched saturated hydrocarbon group of 1 to about 12 carbon atoms, such as methyl, ethyl, *n*-propyl, isopropyl,

n-butyl, isobutyl, *t*-butyl, octyl, decyl, and the like, as well as cycloalkyl groups such as cyclopentyl, cyclohexyl and the like. The term "lower alkyl" intends an alkyl group of 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms.

The term "aryl" as used herein, and unless otherwise specified, refers to an aromatic species containing 1 to 3 aromatic rings, either fused or linked, and either unsubstituted or substituted with 1 or more substituents typically selected from the group consisting of lower alkyl, lower alkoxy, halogen, and the like. Preferred aryl substituents contain 1 aromatic ring or 2 fused or linked aromatic rings.

The term "aralkyl" refers to an alkyl group with an aryl substituent.

THE SUSTAINED RELEASE FORMULATIONS:

In a first embodiment, the invention provides a sustained release pharmaceutical formulation for oral administration, comprising a therapeutically effective amount of a pharmacologically active agent and a carrier selected from the group consisting of solid polyethylene glycols, ingestible waxes, and mixtures thereof, wherein the active agent has a melting point above the melting point of the carrier, and further wherein the active agent is chemically stable at the melting point of the carrier. Preferably, the formulation is a tablet containing approximately 10 wt.% to 85 wt.% active agent, approximately 10 wt.% to 85 wt.% carrier, and, optionally, one or more additives as will be described in detail below.

The pharmaceutical formulation is free of cellulose and cellulose derivatives. Although not wishing to be bound by theory, it appears that the absence of cellulose and cellulose derivatives prevents the tablets from absorbing substantial amounts of water. Consequently, tablets free of cellulose and cellulose derivatives do not swell and remain stable in humid environments.

The carrier may comprise any form of polyethylene glycol (PEG) that is solid at room temperature. Generally, PEGs of a molecular weight grade between 1000 and 8000 may be employed, including, but not limited to, PEG 1000, PEG 1450, PEG 1540, PEG 2000, PEG 3000, PEG 3350, PEG 4000, and PEG 4600 and mixtures thereof. In some instances it may be desirable that the molecular weight of the PEG be above 6000. The hydrophobicity of PEGs decreases with increasing molecular weight and melting temperature.

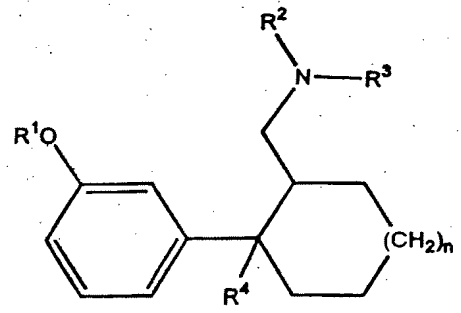
The carrier may also comprise an ingestible wax, including, for example, carnauba wax, hydrogenated castor oil, glyceryl palmitostearate and candelilla wax, with carnauba wax most preferred. Other ingestible waxes include alcohols that are solid at room temperature, preferably having a melting point of at least about 46°C, e.g., cetyl alcohol.

Optimally, the carrier consists essentially of a mixture of approximately 20 wt.% to 60 wt.% of at least one ingestible wax and approximately 2 wt.% to 40 wt.% of at least one solid polyethylene glycol. In this case, the PEG acts as a water-soluble co-melt component to provide hydrophilic channels within the water-insoluble ingestible wax matrix. By adjusting the amounts and grades of PEGs in the matrix, the most desirable dissolution profiles can be obtained.

A preferred sustained release formulation herein is a tablet consisting essentially of 15 wt.% to 70 wt.% active agent, 25 wt.% to 50 wt.% carnauba wax, 2 wt.% to 30 wt.% polyethylene glycol and 5 wt.% to 15 wt.% additives. A particularly preferred sustained release formulation herein is a tablet consisting essentially of 20 wt.% to 40 wt.% active agent, 30 wt.% to 50 wt.% carnauba wax, 5 wt.% to 25 wt.% polyethylene glycol and 5 wt.% to 15 wt.% additives. The sustained release formulations are explained below in detail.

An exemplary formulation contains an active agent useful as an analgesic, the active agent having the structural formula (I)

(I)



wherein: R^1 is C_1-C_3 alkyl or aralkyl, particularly phenyl lower alkyl, such as benzyl or phenethyl; R^2 and R^3 are C_1-C_6 alkyl, aralkyl, particularly phenyl lower alkyl, or R^2 and R^3 together with the nitrogen atom to which they are bound, form a morpholine or pyrrolidine ring; R^4 represents hydroxyl, halogen, or lower alkanoyloxy, particularly C_1-C_6 alkanoyloxy;

and n is 0, 1 or 2, or a pharmaceutically acceptable acid addition salt thereof. It will be recognized, of course, that when R^1 is methyl, R^2 and R^3 are methyl, R^4 is hydroxyl and n is 1, the compound is tramadol. See, e.g., U.S. Patent No. 3,652,589 to Flick et al.

For such amine-containing active agents, the compounds will typically be incorporated in the present formulations in the form of an acid addition salt, which may be prepared from the free base using conventional means involving reaction with a suitable acid. Suitable acids for preparing acid addition salts include both inorganic acids, e.g., hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, as well as organic acids, e.g., acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, etc.

The active agents may be modified in other ways as well, as will be appreciated by those skilled in the art. Depending on the active agent, pharmacologically acceptable esters, amides, prodrugs, conjugates other derivatives may be desirable.

With tramadol formulations, it may be desirable to include one or more additional active agents, as explained in U.S. Patent No. 3,652,589 to Flick et al. Particularly suitable combinations are those with other analgesics such as with acetylsalicylic acid, phenacetin or the like; with antiphlogistic and antiinflammatory agents; with analeptics; with antihistaminic agents; with spasmolytic agents; with muscle relaxants; and with sedative agents.

It is preferred that the formulation be a dosage form containing a unit dosage of the active agent. For tramadol hydrochloride, suitable unit dosages are in the range of approximately 25 to 100 mg, with preferred unit dosages in the range of approximately 50 mg to 75 mg.

Optional additives present in the drug-containing tablets include, but are not limited to, diluents, binders, lubricants, disintegrants, stabilizers, surfactants, coloring agents, and the like. Diluents, also termed "fillers," are typically necessary to increase the bulk of a tablet so that a practical size is provided for compression. Suitable diluents include, for example, dicalcium phosphate dihydrate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, hydrolyzed starches, silicon dioxide, titanium

oxide, alumina, talc, and powdered sugar. Binders are used to impart cohesive qualities to a tablet formulation, and thus ensure that a tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose, lactose, mannitol and sorbitol), polyethylene glycol, waxes, natural and synthetic gums, e.g., acacia, tragacanth, sodium alginate, polyvinylpyrrolidone and Veegum, and synthetic polymers such as polymethacrylates and polyvinylpyrrolidone. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, magnesium stearate, calcium stearate, stearic acid and glyceryl behenate, and are preferably present at no more than approximately 1 wt.% relative to tablet weight. Disintegrants are used to facilitate tablet disintegration or "breakup" after administration, and are generally starches, clays, algins, gums or crosslinked polymers. Stabilizers are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions. Surfactants may be anionic, cationic, amphoteric or nonionic surface active agents, with anionic surfactants preferred. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfonate and sulfate ions, associated with cations such as sodium, potassium and ammonium ions. Particularly preferred surfactants include, but are not limited to: long alkyl chain sulfonates and alkyl aryl sulfonates such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylhexyl)-sulfosuccinate; and alkyl sulfates such as sodium lauryl sulfate. If desired, the tablets may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

Most preferred additives for inclusion in the present formulations include, but are not limited to: magnesium stearate, as a lubricant; and polyvinylpyrrolidone, lactose, sucrose, mannitol and/or sorbitol, as binders.

The tablets may also be coated with a polymeric material that protects the tablet and prevents immediate release of the active agent upon ingestion. Furthermore, the coat may also slow the dissolution rate and maintain the proper shape of the tablet in the gastrointestinal tract. Maintenance of tablet shape is particularly important since a deformed or compacted tablet may result in "dose dumping," i.e. releasing substantially all of the dose at once. Finally, the tablet coat increases the moisture stability of the tablet.

Suitable polymer coatings include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, hydroxypropyl methylcellulose acetate succinate (HPMCAS), hydroxypropylcellulose, shellac, zein, and acrylic acid polymers and copolymers. It should be emphasized, however, that any cellulosic materials that are present will be in the coating not in the tablet formulation *per se*.

The individual tablets are prepared using conventional means. It is preferred that the wax melting step is performed first, followed by dry blending. A preferred method for forming tablets herein is by direct compression of the drug- and carrier-containing composition, in combination with diluents, binders, lubricants, disintegrants, colorants or the like. Also, for coated tablets, conventional coating procedures and equipment may then be used to coat the tablets. For example, a film coating composition may be applied using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. For detailed information concerning materials, equipment and processes for preparing tablets, reference may be had to *Pharmaceutical Dosage Forms: Tablets*, eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989), and to Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 6th Ed. (Media, PA: Williams & Wilkins, 1995).

THERAPEUTIC METHODS:

The novel formulations are to be administered orally to a mammalian individual within the context of a dosage regimen effective to treat a particular condition or disorder. Typically the active agent in the formulations is an analgesic, and the formulations are thus employed as analgesic compositions and may be used to treat individuals predisposed to or suffering from pain, including, but not limited to, headaches, muscular pain, cancer-related pain, and pain associated with medical procedures such as dental, gynecological, oral, orthopedic, post-partum and urological procedures.

The dosage regimen will generally although not necessarily involve drug administration once or twice daily. The amount of formulation administered will, of course, vary from subject to subject and depend on the particular disorder or condition, the severity of the symptoms, the subject's age, weight and general condition, and the judgment of the prescribing physician. Generally, however, a daily dosage of 100 mg to 600 mg

tramadol hydrochloride is suitable. For other active agents encompassed by the structure of formula (I), the daily dosage will be roughly analogous, and an exact dosage regimen for other active agents will be known to or may be readily determined by one of ordinary skill in the art.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

EXPERIMENTAL:

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmaceutical formulation and the like, which are within the skill of the art. Such techniques are explained fully in the literature.

In the following example, efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental error and deviation should be accounted for. Unless indicated otherwise, temperature is in degrees C and pressure is at or near atmospheric. All reagents were obtained commercially unless otherwise indicated.

EXAMPLE 1

A sustained release tramadol hydrochloride was prepared containing the following components:

Tablet Component	wt., mg (unit tablet)	wt.%
Tramadol HCl	100.00	29.50
Carnauba wax	136.00	40.12
PEG 1450 (flake)	43.00	12.68
PEG 4600 (flake)	25.00	7.37
Lactose anhydrous	12.00	3.54
Talc	18.00	5.31
Magnesium stearate	5.00	1.47
Total	339.00	99.99*

* calculated wt.% total not equal to 100.00 due to rounding.

Carnauba wax, PEG 1450 and PEG 4600 were mixed and melted in a jacketed planetary mixer with a heater temperature setting of 99 °C. Once a homogenous melt was achieved, the tramadol HCl was then added and mixed at the same temperature until a uniform mass resulted. The lactose was then added and mixed at the same temperature to form a uniform mass. With the mixer on, the temperature of the mass was cooled down stepwise until granules formed. The granules were first milled and then mixed with talc and magnesium stearate in a V-blender. The resulting granules were compressed into tablets.

The tablets were then coated with a sealing and color coating formulation containing the following components:

Sealing Component	wt., mg (unit tablet)
HPMC 2910	5.10
Dimethyl Polysiloxane Oil	0.05
Anhydrous Shellac	5.02
Subtotal for sealed coated tablet	349.17

Color Component	wt., mg (unit tablet)
Opadry® White	10.17
Carnauba Wax (polishing agent)	0.02
Total for sealed and color coated tablet	359.34

The tablets were coated using conventional techniques.

EXAMPLES 2-4

Other sustained release formulations of the invention were prepared as indicated in the following tables:

Example 2		Example 3		Example 4	
Ingredient	mg/Tablet	Ingredient	mg/Tablet	Ingredient	mg/Tablet
Tramadol HCl	100.0	Tramadol HCl	100.0	Tramadol HCl	100.0
Cetyl alcohol	160.0	Cetyl alcohol	160.0	Carnauba wax	140.0
PEG 1000 to 8000	24.0	PEG 1000 to 8000	27.0	PEG 1000 to 8000	44.0
Lactose anhydrous	33.0	Lactose anhydrous	30.0	Lactose anhydrous	33.0
PVP	10.0	Talc	9.0	PVP	10.0
Talc	9.0	Magnesium stearate	4.0	Talc	9.0
Magnesium stearate	4.0			Magnesium stearate	4.0

EXAMPLE 5

STORAGE STABILITY — COMPARATIVE TESTING

A comparative stability study was conducted to evaluate the formulation of Example 1 versus the sustained release tramadol formulation available as Tramal® Long 100 (Grunenthal GmbH), described in U.S. Patent No. 5,601,842.

The formulation of Example 1 employs a mixture of carnauba wax and polyethylene glycol (PEG) as the carrier matrix, while Tramal® contains a cellulose-based matrix. When both the formulation of Example 1 and Tramal® were subjected to room temperature at low humidity for three days, both tablets remained stable as shown by the lower tablets in Figures 1a and 1b. However, when Tramal® was subjected to 25 °C and 90% relative humidity in a chamber for 3 days, the composition swelled, broke into layers, and became difficult to swallow without chewing as shown by the upper right tablets in Figures 1a and 1b. But, after three days of exposure to the same conditions of temperature and humidity, the present formulation of Example 1 retained its shape as shown by the upper right tablets of Figures 1a and 1b.

Based on these comparative tests, it is concluded that the presently claimed formulations show a much greater storage stability under humid conditions than do cellulose-based sustained release formulations such as Tramal®.

EXAMPLE 6

DISSOLUTION DATA — COMPARATIVE TESTING

A comparative *in vitro* dissolution study was conducted to evaluate the formulation of Example 1 versus the sustained release tramadol formulation available as Tramal® Long 100 (Grunenthal GmbH), described in U.S. Patent No. 5,601,842. In each case the percent of dissolution of the tramadol HCl after 30 minutes, 60 minutes, 120 minutes, 300 minutes and 720 minutes was substantially the same. The data are presented in Table 1.

TABLE 1

	Example 1 and Figure 1 in US Patent 5601842	Example 4 and Figure 2 in US Patent 5601842	Example 5 and Figure 3 in US Patent 5601842	Reference tablet*	New Composition Example 1
Strength	100 mg	200 mg	200 mg	100 mg	100 mg
Matrix Component	HPMC, Calcium hydrogen phosphate, Silicon dioxide, Magnesium stearate	HPMC, MCC Silicon dioxide Magnesium stearate	HPMC, MCC Silicon dioxide, Magnesium stearate	HPMC, MCC PEG Lactose Propylglycol Talc Silicon dioxide, Magnesium stearate Titanium dioxide	Carnauba wax PEG Lactose Talc Magnesium stearate Coat ingredients***
% released****					
30 minutes	26	23	21	21.9	27.8
60 minutes	39	35	33	34.0	34.8
120 minutes	57	51	49	49.2	47.6
300 minutes	84	79	78	75.6	72.5
720 minutes	99	103	98	99.8	93.2

* Reference tablet: Grunenthal's Tramal® Long 100, lot 1131 HF

** Coated tablet Lot 16-Y01

*** Coat ingredients: HPMC, PEG, titanium dioxide

**** The dissolution method is the same as described in US Patent 5601842.

TABLE 1 (continued)

	New Composition Example 2	New Composition Example 3	New Composition Example 4
Strength	100 mg	100 mg	100 mg
	Tramadol HCL Cetyl alcohol PEG Lactose anhydrous PVP Talc Magnesium stearate	Tramadol HCL Cetyl alcohol PEG Lactose anhydrous Talc Magnesium stearate	Tramadol HCL Carnauba wax PEG Lactose anhydrous Talc Magnesium stearate
% released* 30 minutes 60 minutes 120 minutes 300 minutes 720 minutes	 24.3 31.8 43.0 64.0 90.2	 24.4 32.0 43.3 64.2 94.1	 24.6 32.8 44.2 64.0 91.4

EXAMPLES 7-20

Various formulations according to the present invention were prepared using substantially the same procedures as in Example 1. Dissolution profiles for each were obtained.

Example	7	8	9	10	11
Matrix	Cetyl alcohol 19.96% PEG 1450 4.66%	Cetyl alcohol 33.27% PEG 1450 4.66%	Cetyl alcohol 42.39% PEG 1450 4.52%	Cetyl alcohol 48.48% PEG 1450 7.27%	Cetyl alcohol 51.52% PEG 1450 4.24%
Dissolution (%)					
0.5 hour	41	34	31	27	23
1	54	45	41	33	30
2	71	59	54	44	40
3	81	69	63	52	48
4	87	75	69	58	54
6	93	85	79	66	63
8	97	93	90	74	70
10	98	95	N/A	N/A	76
12	97	96	95	84	80

Example	12	13	14	15
Matrix	Cetyl alcohol 47.06% PEG 1450 7.06% PVP K 90 2.94%	Cetyl alcohol 46.97% PEG 4600 11.21%	Cetyl alcohol 47.4% PEG 4600 13.76% PVP K 90 1.83%	Cetyl alcohol 46.97% PEG 1450 9.09% PEG 4600 6.06%
Dissolution (%)				
0.5 hour	24	24	23	31
1	31	30	30	41
2	42	41	40	53
3	50	48	47	62
4	56	53	53	68
6	65	62	61	77
8	72	68	68	83
10	N/A	N/A	N/A	N/A
12	83	79	78	91

Example	16	17	18	19	20
Matrix	Carnauba Wax 42.42% PEG 1450 13.33%	Carnauba Wax 42.42% PEG 1450 16.36%	Carnauba Wax 40.91% PEG 1450 13.63% PEG 4600 8.18%	Carnauba Wax 40.12% PEG 1450 12.68% PEG 4600 7.37%	Carnauba Wax 48.48% PEG 1450 7.27%
Dissolution (%)					
0.5 hour	25	30	29	29	23
1	32	40	39	37	29
2	43	52	52	49	38
3	50	60	60	58	44
4	56	66	66	64	50
6	64	74	75	73	58
8	72	81	81	78	64
10	N/A	N/A	N/A	N/A	N/A
12	84	89	88	87	74

CLAIMS

1. A sustained release pharmaceutical formulation with reduced sensitivity to moisture, comprising approximately 10 wt.% to 85 wt.% of a pharmaceutically active agent and approximately 10 wt.% to 85 wt.% of a carrier consisting essentially of a mixture of a solid polyethylene glycol and an ingestible wax, wherein the active agent has a melting point above the melting point of the ingestible wax and is chemically stable at the melting point of the ingestible wax.

2. The formulation of claim 1, wherein said carrier consists essentially of a mixture of approximately 20 wt.% to 60 wt.% of at least one ingestible wax and approximately 2 wt.% to 40 wt.% of at least one solid polyethylene glycol.

3. The formulation of claim 2, wherein the ingestible wax is selected from the group consisting of carnauba wax, hydrogenated castor oil, glyceryl palmitostearate, candelilla wax, and mixtures thereof.

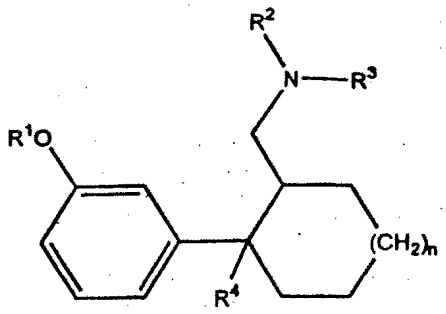
4. The formulation of claim 3, wherein the ingestible wax is carnauba wax.

5. The formulation of claim 1, wherein the ingestible wax is an alcohol having a melting point of at least 46°C.

6. The formulation of claim 5, wherein the alcohol is cetyl alcohol.

7. The formulation of claim 1, wherein the active agent has the structure of formula (I)

(I)



wherein:

R^1 is C_1-C_3 alkyl or aralkyl;

R^2 and R^3 are C_1-C_6 alkyl and aralkyl, or R^2 and R^3 together with the nitrogen atom to which they are bound form a morpholine or pyrrolidine ring;

R^4 represents hydroxyl, halogen, or lower alkanoyloxy; and

n is 0, 1 or 2, or a pharmaceutically acceptable acid addition salt thereof.

8. The formulation of claim 7, wherein:

R^1 is C_1-C_3 alkyl, benzyl or phenethyl;

R^2 and R^3 are C_1-C_6 alkyl or phenyl lower alkyl;

R^4 represents hydroxyl, halogen, or C_1-C_6 alkanoyloxy; and

n is 0, 1 or 2, or a pharmaceutically acceptable acid addition salt thereof.

9. The formulation of claim 8, wherein R^1 is methyl, R^2 and R^3 are methyl, R^4 is hydroxyl and n is 1, such that the active agent is tramadol or a pharmaceutically acceptable acid addition salt thereof.

10. The formulation of claim 9, wherein the active agent is tramadol hydrochloride.

11. The formulation of any one of claims 1, 7 or 10, comprising a unit dosage of the active agent.

12. The formulation of claim 11, wherein the unit dosage is in the range of approximately 25 mg to 100 mg.

13. The formulation of claim 12, wherein the unit dosage is in the range of approximately 50 mg to 75 mg.

14. The formulation of any one of claims 1, 7 or 10, having a coating over said tablet.

15. The formulation of any one of claims 1, 7 or 10, further comprising an additional active agent.

16. The formulation of any one of claims 1, 7 or 10, further comprising approximately 5 wt.% to 15 wt.% of an additive selected from the group consisting of diluents, binders, lubricants, disintegrants, stabilizers, surfactants, coloring agents and combinations thereof.

17. The formulation of claim 16, wherein the additive is selected from the group consisting of magnesium stearate, polyvinylpyrrolidone, lactose, sucrose, mannitol, sorbitol and combinations thereof.

18. A sustained release pharmaceutical formulation consisting essentially of approximately 15 wt.% to 70 wt.% tramadol or a pharmaceutically acceptable acid addition salt thereof, approximately 25 wt.% to 50 wt.% of an ingestible wax, approximately 5 wt.% to 40 wt.% polyethylene glycol having a molecular weight in the range of approximately 1000 to 8000, wherein the melting point of tramadol or the pharmaceutically acceptable acid addition salt thereof is above the melting point of the ingestible wax and is chemically stable at the melting point of the ingestible wax.

19. The formulation of claim 18, wherein the ingestible wax is selected from the group consisting of carnauba wax, hydrogenated castor oil, glyceryl palmitostearate, candelilla wax, and mixtures thereof.

20. The formulation of claim 19, wherein the ingestible wax is carnauba wax.

21. The formulation of claim 18, wherein the ingestible wax is an alcohol having a melting point of at least 46°C.

22. The formulation of claim 21, wherein the alcohol is cetyl alcohol.

23. A method of treating pain in a mammalian subject which comprises the step of orally administering to said subject the pharmaceutical formulation of any one of claims 1, 7, 10 or 18.

Figure 1a

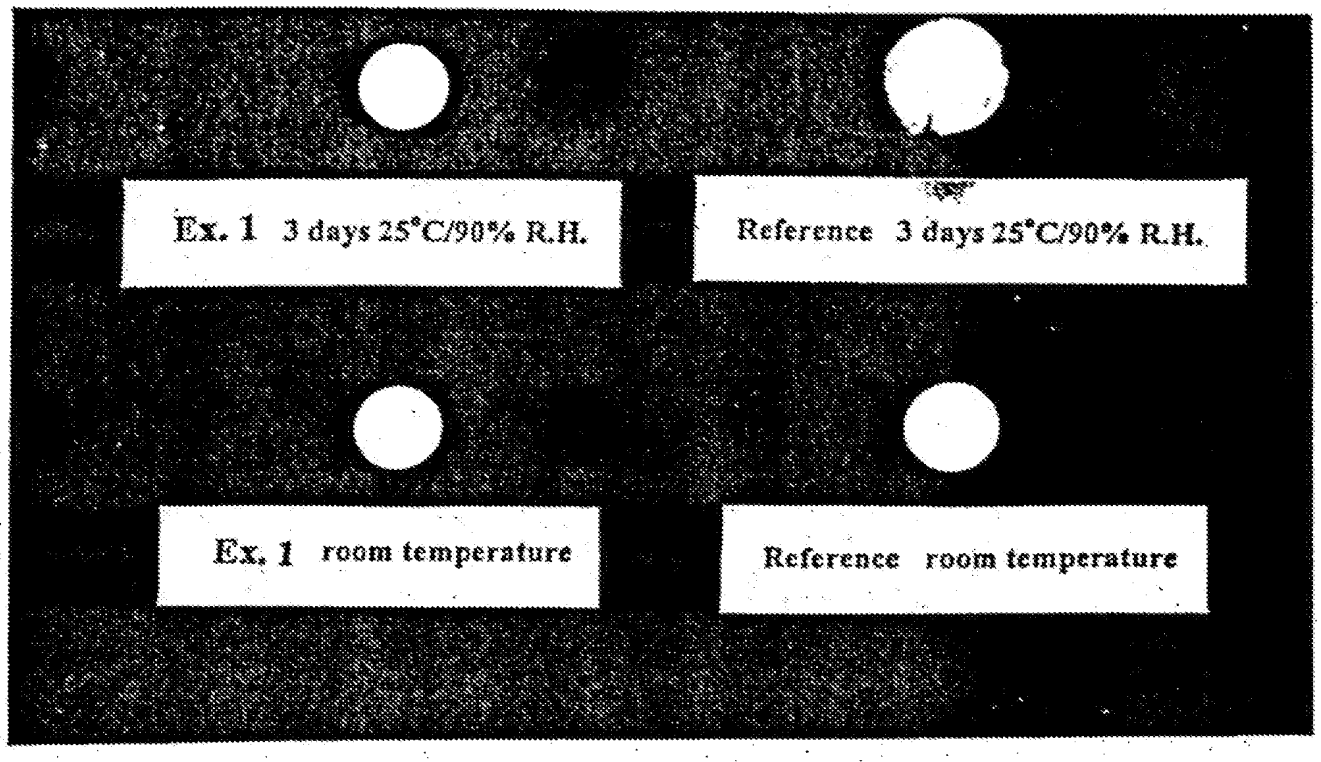


Figure 1b